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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/972,245
Filing Date: October 09, 2001
Appellant(s): ROBERTS ET AL.

R. Brian McCaslin
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/26/2010 appealing from the Office action mailed 6/23/2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application: 1-6, 11-13, 17-22, 41, 42, and 44.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6531122	Pedersen	3-2003
4678812	Bollin	7-1987

Boos *et al.* (Eur. J. Cancer 32A(9) : 1544-1550, 1996)

Kawashima *et al.* (Leukemia Res. 15(6): 525-530, 1991)

Ettinger *et al.* (Cancer 75: 1176-1181, 1995)

Saito *et al.* (Leukemia (1997 Apr) Vol. 11 Suppl. 3, pp. 408-9)

Francis *et al.* (Int. J. Hematol. 68(1): 1-18, 1998)

Abuchowski *et al.* (Cancer Treat Rep 63(6): 1127-1132, 1979)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 stand rejected under 35 USC 103(a) as being unpatentable over the combination of Boos *et al.* (Eur. J. Cancer 32A(9) : 1544-1550, 1996), Kawashima *et al.* (Leukemia Res. 15(6): 525-530, 1991), Ettinger *et al.* (Cancer 75: 1176-1181, 1995), Saito *et al.* (Leukemia (1997 Apr) Vol. 11 Suppl. 3, pp. 408-9), and Francis *et al.* (Int. J. Hematol. 68(1): 1-18, 1998).

Boos studied the effects of using different preparations of unmodified asparaginase from different sources (*E. coli* or *Erwinia*) in the treatment of acute lymphoblastic leukemia because it was known that different asparaginase preparations had pharmacokinetic differences associated with increasing reports of hemorrhagic and thrombotic events. Boos stated that the pharmacologic aim of asparaginase treatment is the maximum reduction of asparagine concentration in patient's blood (page 1544, right column, lines 1-4), and made asparaginase activity the primary parameter for monitoring the effect of the drug on patients (page 1545, left column, lines 13-19). Patients were administered multiple doses of either of two *E. coli* asparaginase preparations, or of an *Erwinia* preparation, and asparaginase activity was assayed both

before and after each administration. Boos established that the different preparations were not interchangeable, and found that each of the preparations provided different levels of activity after administration. See abstract and Figs. 1-4. Thus Boos provided a template and motivation for comparing the effects and activities of different preparations of asparaginase *in vivo*. At least some of the patients of Boos were clearly immunocompetent in view of the fact that they had allergic responses (see abstract). In view of the fact that people in general are immunocompetent, it would have been obvious to one of ordinary skill in the art to have practiced the method of Boos on immunocompetent patients. Similarly to the claims, Boos rendered obvious a method including the steps of:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first therapeutic agent after said first therapeutic agent has been administered to said first immunocompetent subject;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first therapeutic agent after a second dose of said first therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second therapeutic agent after said second therapeutic agent has been administered to said second immunocompetent subject, wherein said second therapeutic agent is different from said first therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second therapeutic agent after at least one booster

dose of said second therapeutic agent has been administered to said second immunocompetent subject; and

(e) comparing the biological activity of said first therapeutic agent with the biological activity of said second therapeutic agent.

Boos did not teach a comparison of biological agents that had been modified with a biocompatible polymer, and did not explicitly address host-mediated inactivation.

Kawashima reported on the treatment of patients with hematological malignancies with 2, 4 - bis(*o*-methoxypolyethylene glycol)-6-chloro-S-triazine-conjugated L-asparaginase (PEG_2-ASP). One patient, suffering non-Hodgkin's lymphoma, received treatment with unmodified L-asparaginase and suffered severe nausea, vomiting and loss of appetite. The patient went into remission, but later relapsed and was then treated with weekly or twice weekly intravenous infusions of PEG_2-ASP, leading to complete remission within 2 months. The patient remained in complete remission for over one year with weekly infusions of PEG_2-ASP. During this period blood asparagine was assayed but was not detectable. Serum levels of asparaginase activity were measured throughout the course of treatment, before and after multiple administrations of PEG_2-ASP. See Fig. 1 on page 527 and Figs 2 and 3 on page 528. So, Kawashima taught a method of determining enzyme activity of a modified asparaginase in serum derived from blood samples before, after, and between, multiple administrations of the drug. Determination of the asparaginase activity in serum is considered to be an assay of the asparaginase activity in the blood sample.

Ettinger reported the results of a multi-center study of monomethoxypolyethylene glycol succinimidyl)74-L-asparaginase (Oncaspar or PEG-L-asparaginase). Patients suffering from acute lymphoblastic leukemia, who had previously been treated with unmodified L-asparaginase, received PEG-L-asparaginase at days 1 and 14 of treatment. Two thirds of evaluable patients achieved complete remission. See Fig. 1 on page 1177, and page 177, column 2, under "Clinical Laboratory Evaluation", and "Response Criteria". See also page 1178, column 1, last two paragraphs.

Saito compared the antitumor activities of unmodified L-asparaginase and L-asparaginase modified with a comb-shaped copolymer of polyethylene glycol and maleic anhydride (PM-asparaginase). Mice were inoculated intraperitoneally with murine lymphoma cells, and then received unmodified L-asparaginase or PM-asparaginase. Five out of six mice treated with PM-asparaginase were alive at day 60 and were free of tumors. PM-asparaginase had increased antitumor activity relative to unmodified asparaginase. See paragraph bridging pages 408 and 409.

Francis taught that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be affected by the way in which the protein drug is PEGylated. See abstract, and pages 2-4. Francis also taught that PEGylation of protein drugs can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally

determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a PEGylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

So, the prior art taught that the type and extent of PEGylation of therapeutic proteins could affect their enzymatic activity and immunogenicity, such that it would be obvious to optimize these variables (see Francis and Saito above), and that PEGylation can also affect the bioavailability of the protein (see Ettinger at e.g. page 1176, column 2, second full paragraph of introduction). The cited prior art also taught three different forms of modified L-asparaginase (Kawashima, Ettinger, and Saito, respectively), each modified differently with a polyethylene glycol or a polyethylene glycol derivative, as well as templates for comparing different preparations of asparaginase (Boos, Saito). In one template (Saito), antitumor activity was measured as the endpoint. The other template (Boos) was designed to address proper dosing, and measured enzymatic activity. Kawashima also taught a protocol in which pegylated asparaginase was administered repeatedly, and activity was assayed from serum samples before and after multiple administrations (Fig. 1 on page 527 and Figs 2 and 3 on page 528).

Given that all three forms of L-asparaginase discussed above had anticancer activity, and that it was known that differently modified enzymes often had different pharmacokinetic characteristics such as activity and half-life, as well as different immunoreactivities, it would have been obvious to one of ordinary skill in the art at the

time of the invention to compare each of these modified asparaginases to determine which preparation was most efficacious for treating cancer, just as Saito had compared modified and unmodified asparaginases. Although Saito did not measure enzyme activity in that comparison, it was clear from the teachings of Boos and Kawashima that it was routine in the art to measure blood asparaginase activity over the course of asparaginase treatments. Moreover, one would have been motivated to do so because the presence of asparaginase catalytic activity is what provides the therapeutic effect of asparaginase treatment (see Boos above). One would have been further motivated to perform such a comparative study because Saito taught that differentially modified asparaginases had different performance characteristics, i.e. Saito taught that PM-asparaginase reduced immunoreactivities at lower degrees of modification than PEG_2-asparaginase. See Introduction on page 408. Because, one of ordinary skill appreciated that different modifications may lead to differences in enzyme activity, immunoreactivity, and circulation time (see Francis and Ettinger, above), it would have been obvious to perform comparisons of activity *in vivo*, as exemplified by Boos, when comparing differently modified asparaginases.

If one compared treatment protocols with two differently modified asparaginases, and measured blood asparaginase activity as taught by Boos and Kawashima, then one would have carried out the same active method steps that Applicant claims. By carrying out these method steps, one would have inherently fulfilled the purpose set forth in the preamble, i.e. determining the type of biocompatible polymer, extent of modification, and conditions for modification of a therapeutic agent to prevent host-mediated

inactivation of said therapeutic agent. Note that in comparing the activities of two differently pegylated asparaginases, it would have been obvious to determine which one was more active over the course of treatment because it is in the best interest of future patients to do so.

Note also that the step of (e) of claim 1 and step (f) of claims 42 and 44 require a comparison of the assayed biological activities "to select" the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of the therapeutic agent. Thus the claims literally require that to select the type of biocompatible polymer, extent of modification, and conditions for modification that prevent host-mediated inactivation, one compares the biological activity of the two differently modified therapeutic agents. In one reasonable interpretation of the claim, the selection is a mental process accomplished by identifying the better performer on the basis of the comparison. It would have been obvious to identify the most active asparaginase in a comparison of differently modified asparaginases because activity correlates with therapeutic effect. In identifying, the more active asparaginase, one would inherently have identified the one that suffered the least host-mediated inactivation, so this step would inherently render obvious steps (e) of claim 1 and step (f) of claims 42 and 44.

Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the

optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph. Accordingly, it would be obvious to determine the relative catalytic activity of differently modified versions of L-asparaginase over the course of treatment, because there was reason to believe that some versions might be more or less active than others, and because it was routine in the art to make such measurements, as evidenced by Boos and Kawashima.

Claim 4 stands rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Pedersen *et al.* (US 6,531,122, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also taught that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Pedersen taught that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used

interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, it was apparent from the teachings of Francis that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be differentially affected by the way in which the protein drug is PEGylated. See abstract. Thus it would have been obvious to use different linkages in the process of optimizing these result-effective variables.

Thus the invention as a whole was prima facie obvious.

Claim 8, 11, and 20-22 stand rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Abuchowski *et al.* (Cancer Treat Rep 63(6): 1127-1132, 1979).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Abuchowski taught treatment of tumors in mice by administration of *Achromobacter* glutaminase asparaginase rendered nonimmunogenic by modification with polyethylene glycol. The resulting enzyme had greatly enhanced half life in blood and increased the survival of experimental mice inoculated with tumor cells when compared with unmodified glutaminase asparaginase. Abuchowski measured asparaginase activity in blood over time after a single injection of enzyme, and also measured mouse weight throughout the course of treatment in which mice were given PEGylated enzyme on alternate days. See Figures 3 and 4 on pages 1130 and 1131.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further study and compare differently modified *Achromobacter* glutaminase asparaginases in the process of optimizing PEGylation of this enzyme. One would have been motivated to do so because it was clear to those of ordinary skill in the art at the time of the invention that the amount and type of PEGylation was a result effective variable that influenced the activity of the enzyme as well as its serum half life and immunogenicity, as taught by Francis. In doing so it would have been obvious to determine the activity of the differently modified drugs by assay of catalytic activity as taught by Boos, Kawashima, and Abuchowski. In comparing the performance of two

differently modified enzymes over the course of treatment, one of ordinary skill would practice all of the claimed method steps, such that the invention as claimed would have been obvious.

Claim 19 stands rejected under 35 USC 103(a) as being unpatentable over Boos, Kawashima, Ettinger, Saito, and Francis as applied to claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41, 42, and 44 above, and further in view of Bollin *et al.* (US 4,678,812, of record).

The teachings of Boos, Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

(10) Response to Argument

Appellant asserts at page 9 of the Brief that the examiner has pointed to "diverse aspects of various published documents with no apparent rationale for combining them in the fashion claimed, save appellant's own disclosed insights." At page 11, appellant asserts that the examiner has arrived at the claimed invention through hindsight reconstruction, relying on "the very insight that appellant's own discovery illuminated", that discovery being the use of enzymatic activity as the metric by which to optimize the protection of an enzymatic therapeutic agent from host-mediated inactivation.

These assertions are incorrect. In fact, the Examiner has shown over the course of prosecution that the method steps claimed by appellant would have been obvious to perform without specific regard for measuring host-mediated inactivation *per se*. The Examiner has relied on MPEP 2144 (IV) to support the position that the reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It would have been obvious to carry out the active steps of the claimed method in the process of comparing the efficacies of two differently modified asparaginases for treating cancer. It was accepted in the prior art that the enzymatic activity of asparaginase was responsible for its therapeutic effect, and so when comparing two different asparaginase preparations, it was obvious to measure their activities over the course of treatment. Therefore, in accomplishing the active method steps, one of ordinary skill would have inherently achieved the purpose set forth in the preamble regarding identifying the modification parameters that prevent host-mediated inactivation. Thus, the rejections do not depend on any insight

regarding host-mediated inactivation, and were not constructed through hindsight. Instead the rejections were based on the art-recognized interest in using asparaginase to treat cancers, the recognized advantages of pegylating asparaginases, the existence of differently pegylated forms of asparaginase, the recognition that different types of modifications had different effects on *in vivo* performance characteristics such as activity, and the motivating desire to determine which form of pegylated asparaginase performed the best in treating a cancer.

Applicant argues at page 10 that the Examiner cherry-picked various steps used to determine the modification conditions from among countless combinations, when nothing in the cited record suggests which parameters are critical or which of many possible choices is likely to be successful for determining the modification conditions of a therapeutic agent to prevent host mediated inactivation to a method of the therapeutic agent. This is unpersuasive because it would not have been necessary for an artisan to have contemplated a method of determining the modification conditions of a therapeutic agent to prevent host mediated inactivation in order to have combined the references in such as way as to render the claims obvious. One would have been motivated to combine the cited art in order to determine which of two or more differently modified asparaginases performed the best in treating cancer. In studying the effects of such drugs, it was routine to perform asparaginase assays over the course of treatment, between drug administrations, as shown by Boos and Kawashima. The Examiner provided an example of researchers (Boos *et al.*) comparing different asparaginase preparations known to have different pharmacological characteristics, in which the

researchers measured asparaginase activities throughout the course of treatment. The Examiner provided examples of several differently modified asparaginases (Kawashima, Ettinger, and Saito), and also showed that it was known that the type and extent of modification can affect enzyme activity and other performance characteristics (Francis, Saito). So, one of ordinary skill would reasonably have expected differently modified asparaginases to have different pharmacokinetic parameters, possibly requiring different dosing regimens, and would have been motivated to compare them. It would also have been obvious to measure several outcomes, such as asparaginase activity, blood asparagine levels, and the amounts of various blood cells, but this does not mean that it would not have been obvious to measure enzyme activity throughout the course of treatment, as taught by Boos and Kawashima. Note that Kawashima performed all of these assays (blood asparagine, blood asparaginase, and levels of various blood cells), such that one of ordinary skill would have considered performance of all of them to be routine, *i.e.* no selection of any one assay would have been required.

At page 11 of the Brief, appellant reviews the Boos reference, characterizing it as an evaluation of the known variability in activity among different commercial preparations of asparaginase by measuring asparaginase activity during the course of cancer treatment, thereby formulating dosing requirements for each different preparation. Appellant asserts that it is unsurprising that a practitioner would formulate dose-response curves in an effort to formulate a uniform dosing regimen for an enzymatic therapy. The Examiner agrees, and notes that in fact Boos formulated comparative does response relationships for at least two different forms of

asparaginase. This would have been obvious to do for any two or more differing forms of asparaginase, including those disclosed by Kawashima, Ettinger, and Saito. It is simply in the best interest of patients to do so.

Appellant asserts at page 11 that the examiner has contended that testing should occur in a preclinical setting. This is incorrect. The rejection indicates simply that it would have been obvious to compare differently modified forms of asparaginase because it was recognized in the prior art that differently modified forms had different performance characteristics. Clearly there was an interest in treating certain cancers with asparaginase, and there were differently modified forms of asparaginase available for use, such that it would have been obvious to compare differently modified forms to determine which was the most efficacious. Enzymatic activity is obviously required for therapeutic activity, so it would have been obvious to measure enzymatic activity over the course of treatment as was taught by Kawashima and Boos. It would have been obvious to make such a comparison in either a preclinical setting (such as an animal model) or in a clinical setting because it was routine in the prior art to study the activities or effects of asparaginases in both preclinical (Saito) and clinical (Kawashima, Ettinger, and Boos) settings.

Appellant asserts at page 11 that the conventional wisdom regarding therapeutic protein optimization focused on shielding the protein from the immune system and increasing the protein's stability, and that this was performed *in vitro* in the prior art (relying on the Chinol, Deckert, and Alvarez references). In contrast, it is asserted that it was appellant's own insight to optimize modification of therapeutic enzymes by

evaluation of enzyme activity *in vivo*. Appellant asserts at page 12 that the examiner has attempted to use appellant's insight, as well as creative claim construction, to transform the claimed invention from its developmental setting to that of a clinical setting.

To the extent that Applicant's argument relies on any distinction between clinical and preclinical settings it is unpersuasive because the claims do not recite any limitations regarding clinical or preclinical settings.

Appellant's assertion that the claimed invention was not obvious because optimization of therapeutic enzymes by evaluation of enzyme activity *in vivo* was unknown in the prior art is unpersuasive. The measurement of pegylated asparaginase activity in blood before and after repeated administrations over the course of cancer treatment was routine in the prior art (see Kawashima), as was the concept of measuring activity of different forms of asparaginase before and after repeated administrations, over the course of cancer treatment (see Boos). Moreover, it was clear in the prior art that there was an interest in comparing different forms of asparaginase in cancer treatment (see Saito). There was prior knowledge that differently modified forms of asparaginase had different *in vivo* performance characteristics (Saito and Francis). Therefore it would have been obvious to compare differently modified asparaginases *in vivo* to see which one worked best. Because it was known that therapeutic efficacy depended on enzyme activity (Boos) it would have been obvious to measure enzyme activity over the course of treatment as taught by

Boos and Kawashima, even if one was not specifically concerned with host-mediated inactivation.

At pages 12 and 13 appellant addresses the issue of the patentable weight accorded to the selection step in item (e) of claim 1 and item (f) of claims 42 and 44. This step is essentially as follows:

> comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer

In the rejection, this step was considered to be inherent in the active step of comparing the agents to determine which has the greater asparaginase activity over the course of treatment. The claim literally requires that to select the type of biocompatible polymer, extent of modification, and conditions for modification that prevent host-mediated inactivation, one compares the biological activity of the two differently modified therapeutic agents. Thus it appears that in performing this comparison, the selection step is accomplished. Even if one argued that the selection step must be a separate step that is possible only after comparing the data, such a step would have been obvious inasmuch the determination of which agent was superior was the entire point of making the comparison. The prior art interest in using asparaginase to treat cancers, the recognized advantages in modifying asparaginases, and the recognition that differently modified asparaginases have different performance characteristics combined to make it obvious prior to the time of the invention to compare differently modified asparaginases to see which one performed the best. There is no point in making the comparison if one does not then select the best performer.

Appellant also addresses the issue of the patentable weight of the preamble's stated objective of “determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer". Appellant correctly notes that the determination of whether a preamble limits a claim is made on a case-by-case basis. Appellant asserts that the preamble gives meaning and purpose to the recited manipulative steps, arguing that in the absence of the preamble’s stated objective the recited "assaying" and "comparing" terms resolve to mere academic exercises with little meaning or utility. This is unpersuasive. The cited references render obvious a method of determining which of two differently modified asparaginases is more effective for treating a cancer. In view of the cited art, in particular Saito and Francis, it was known that different types of modification can have different effects on enzyme characteristics *in vivo*, including activity, half life, and immunogenicity. It was known, particularly in view of Boos, that the pharmacologic aim of asparaginase treatment is the maximum reduction of asparagine concentration in patient's blood (Boos at page 1544, right column, lines 1-4), and that asparaginase activity is an important parameter for monitoring the effect of the drug on patients (Boos at page 1545, left column, lines 13-19). Accordingly, it would have been obvious to measure the activities of differently modified asparaginases over the course of treatment, before and after each of multiple administrations, as exemplified by Boos and Kawashima. One may deem the interest in tracking asparaginase activity over the course of treatment to be an academic exercise,

but it clearly would have meaning and utility in view of the teachings of Boos and Kawashima, or it would not have been undertaken in these studies.

The issue of the weight of the preamble's stated objective reduces to whether or not the preamble's intended use limitation "to prevent host-mediated inactivation" distinguishes over the prior art. MPEP 2111.02 (II) indicates that, for process claims, the claimed invention must be evaluated to determine whether the recited purpose or intended use results in manipulative difference between the claimed invention and the prior art. In this case there is no manipulative difference between the claims and the prior art. The manipulative steps involve assaying blood samples for enzyme activity after administration of first and second differently modified therapeutic agents to respective first and second immunocompetent hosts, repeating this step after a second administration of each agent, and comparing the enzyme activities of the first and second agents. Each of these steps is obvious in view of the cited art for the reasons set forth at length above. There is no manipulative step that is affected in any way by the preamble's recitation of the intended use "to prevent host-mediated inactivation". Note that the step "to select the type of biocompatible polymer", etc., recited in items (e) and (f) of claims 1 and 44, respectively, is accomplished by the step of comparing the biological activity of the modified agents, as discussed above.

At pages 13-15 of the Brief, appellant argues that the examiner has not shown apparent reason to have combined the various prior-art elements in the fashion claimed with the requisite expectation of success.

Appellant asserts that the Federal Circuit has found non-obviousness where the claims at issue were directed to a specific chemical compound and the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation, citing *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.,* 492 F.3d 1350 (Fed. Cir. 2007).

Appellant drew an analogy with the *Takeda* case, asserting that the cited references disclose a number of possible steps but provide no reason for selecting the particular combination of appellant's claimed methodology. As an example, Appellant indicates that the cited references teach a variety of ways for gauging the biological activity of a modified therapeutic agent, relying for support on the Declaration of Dr. Sethuraman. This Declaration is directed to the issue of what one of skill in the art would consider to be suitable as an assay for measuring enzymatic activity of a modified asparaginase. Appellant also asserts that the cited art presents myriad timing options for conducting measurements.

Appellant's arguments regarding the alleged myriad timing options are unpersuasive because appellant does not point to any timing options in the cited art other than those taught by Boos and Kawashima, *i.e.* the same timing pattern that is claimed instantly.

Appellant's arguments regarding the variety of ways for gauging the biological activity of a modified therapeutic agent are unpersuasive as well. The Declaration of Dr. Sethuraman indicates that gauging asparaginase activity by measuring erythrocytes, lymphoid cells, granulocytes, blast cells, leukemic blasts, hypocellularity of bone

marrow, or peripheral blood counts can lead to false negatives, such that these measures would be unsatisfactory. This is unpersuasive because, as stated at page 16 above, Kawashima used all of these assays as well as measuring blood asparaginase levels, in order to assess the patient's progress. See Kawashima at Fig. 1 on page 527, and Figs. 2 and 3 on page 528. Accordingly it would have been obvious to use all of them, including asparaginase activity measurement, in the determination of which modified asparaginase performed best.

Appellant's analogy to the *Takeda* case is also unpersuasive. In *Takeda* the cited prior art disclosed lead compounds from which, the court decided, it would not have been obvious to arrive at the claimed compound. Appellant drew an analogy between these lead compounds and the various possible assays disclosed in the cited art. However, the teachings of Kawashima would have led one of ordinary skill to assay all of the variables assayed by Kawashima, including asparaginase activity, when analyzing the usefulness of one or more variants of asparaginase. Thus, by appellant's analogy, it would have been obvious to select all of the lead compounds for further use. Kawashima shows that it was within the level of ordinary skill in the art to do so. Furthermore, the Boos reference provides motivation to measure asparaginase activity specifically, because it is the "primary parameter" for monitoring the effect of the drug on patients in that study (see page 1545, left column , lines 17-19). Thus there was clear motivation in the cited art to assay asparaginase activity in methods of evaluating asparaginase efficacy, and appellants arguments based on the declaration of Dr. Sethuraman and the analogy to *Takeda* are unpersuasive.

Appellants arguments at pages 15-16 rely on the arguments set forth in pages 10-15, and are unpersuasive for the reasons set forth above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Richard Schnizer/

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